201-14294A

Response to EPA Comments on Chemical RTK HPV Challenge Submission:
Thiodipropionates Category

The sponsor of the thiodipropionate category, the Thioesters Association, thanks EPA for their comments. Below are specific responses to comments raised by EPA.

Response to specific EPA comments in the Test Plan

In the test plan (Matrix table, page 2/23 and Table 6, page 16/23), the submitter estimated a NOAEL of ~1125 mg/kg/day for 0.400 kg Fisher rats exposed to 3% 3,3'-thiodipropionic acid dioctadecyl ester in feed for two years. The submitter needs to provide the details of this calculation.

> The study by Tullar conducted between 1944 and 1947 did not supply sufficient information to accurately convert percentage test material in the feed to mg/kg/day as routinely used today. The only information supplied by Tullar was the average feed consumed/rat/day (19,800 mg/rat/day) for the entire study and the average weight at selected time points. The highest average body weight for the group receiving 3% in the diet was 390 grams. If one uses these two values, the value would be 1523 mg/kg/day. However, the use of the average feed consumption for the entire study may not be appropriate.
>
> Thus, rather than report this value in the test plan, control data from representative studies with F-344 rats of 400 grams which have an average daily feed intake of 15 g was used. These rats have a comparable body weight to those used by Tullar. This results in a value of approximately 1125 mg/kg/day. This results in a lower predicted NOAEL.

Response to specific EPA comments on the Robust Summaries

General Comments
The IUCLID data set for 3,3'-thiodipropionic acid dioctadecyl ester did not list the purity of the compound.

> The purity information has been added to Section 1.1-1.4

The IUCLID data set for 3,3'-thiodipropionic acid ditridecyl ester lists the wrong CAS. No. in the id header on pages 14/37-22/37

> The reason for the change in CAS number in the IUCLID data set is unknown. This has been changed.

Health Effects
Acute Toxicity
3,3'-Thiodipropionic acid didodecyl ester. The three olive oil vehicle studies did not report the length of the observation period or indicate whether the animals were evaluated for systemic effects aside from mortality.

> An occasional data point was missed. This has been added whenever possible.

3,3'-Thiodipropionic acid dioctadecyl ester. The submitter submitted data for four acute toxicity studies (3 in rats and 1 in mice). Information omitted included the gavage vehicle, the length of the observation period, and results for systemic toxicity.

> An occasional data point was missed. This has been added whenever possible.

Repeated-Dose Toxicity.

3,3'-Thiodipropionic acid didodecyl ester. The robust summary did not report the gavage vehicle or the specific differences in outcomes following exposure at the NOAEL (350 mg/kg/day) and the NOEL (125 mg/kg/day).

> The robust summary has been updated. The gavage vehicle was 1% carboxymethyl cellulose in water. The following provides the specific outcomes of exposure at 350 and 125 mg/kg/day and the basis for the NOAEL and NOEL.
>
> At the 350 mg/kg/day dose:
>
> HAEMATOLOGY:
>
> Females at this dose exhibited a very small, but not statistically significant, increase in Hb concentrations. These individual values fell with in the normal background range are considered unlikely to be a direct toxic effect of the test material.
>
> CLINICAL CHEMISTRY: Calcium concentrations of the males were slightly elevated compared with controls. However, the differences were small, not statistically significant and generally well with in the normal background range.
>
> Based on this information, it was concluded that none of these findings were adverse, therefore, the NOAEL was noted as 350 mg/kg/day.
>
> None of these findings or any other abnormal findings were noted at the 125 mg/kg/day level, thus the NOEL.

3,3'-Thiodipropionic acid dioctadecyl ester. The robust summary for the 2-year feeding study omitted the animals' sex and incidence data for the observed body weight effects. Also, the summary did not include the submitter's estimation of daily dose (mg/kg/day) that was reported in the test plan (tables on pages 2/23 and 16/23).

> The robust summary has been updated. Male rats were used. Selected body weight incidence data at 90 day intervals has been included. Estimation of daily dose has been covered previously in response to test plan.

Genetic Toxicity.

3,3'-Thiodipropionic acid didodecyl ester. The robust summary for mutation in bacterial cells did not report the positive control or the source of the S9 used for metabolic activation.

> The robust sumary has been updated to include the source of the S9 and positive controls used.

The robust summary for the *in vivo* micronucleus assay in rats did not report whether there was any effect on the mitotic index.

> The robust summary has been updated. There was no effect on the mitotic index.

3,3'-Thiodipropionic acid dioctadecyl ester. The robust summaries for both studies did not report the source of the metabolic activation system and the purity of the test material.

> The source of the metabolic activation system is supplied for both studies. The purity of the test material was >95% for both studies.

Reproductive Toxicity. 3,3'-Thiodipropionic acid didodecyl ester. The robust summary did not state the gavage vehicle.

The gavage vehicle was reported as 1% carboxymethyl cellulose in water.

Developmental Toxicity. 3,3'-Thiodipropionic acid didodecyl ester. Robust summaries for all four studies were complete except for the gavage vehicle and the purity of the test substance.

Test material was administered as a corn oil solution. No information was provided on purity of test material.